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Frontiers in Research Review:

Ambulatory and Home Blood Pressure Measurement in the Management of Hypertension

Blood pressure variability in risk stratification: What does it add?

Kei Asayama,*† Rudolph Schutte,‡ Yan Li,§ Tine W Hansen¶ and Jan A Staessen***

**Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, KU Leuven, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium, †Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences Sendai, Japan, ‡Department of Physiology, Hypertension in Africa Research Team, North-West University Potchefstroom, South Africa, §Center for Vascular Evaluation Shanghai Institute of Hypertension Ruijin Hospital Shanghai Jiaotong University School of Medicine Shanghai, China, ¶Steno Diabetes Center Gentofte, Denmark and **Department of Epidemiology, Maastricht University Maastricht, The Netherlands*

SUMMARY

1. In this minireview we address the predictive value of blood pressure variability, over and beyond level of pressure, in randomly selected population samples. All reviewed studies had sufficient power, long follow-up duration and a wide age range.

2. We assessed blood pressure variability derived from home visit, self-measured home pressure and 24 h ambulatory monitoring. The conclusions are based mainly on novel indices of blood pressure variability: variability independent of the mean, difference between maximum and minimum blood pressure and average real variability.

3. None of these variability indices or morning surge in blood pressure substantially refined risk profiling over and beyond the blood pressure level.

4. In risk stratification, clinicians should concentrate on blood pressure level, the predominant risk factor modifiable by lifestyle measures and antihypertensive drug treatment.

Key words: average real variability, blood pressure variability, epidemiology, general population, risk factors, variability independent of the mean index.

INTRODUCTION

The prognostic significance of blood pressure variability (BPV) remains contentious. Some studies have reported associations between BPV and end-organ damage,[1–4] cardiovascular events[5–7] or mortality[8], whereas others failed to do so or found variability to be inferior to mean systolic pressure.[9–11] Whether naturally occurring BPV predicts risk over and beyond blood pressure level remains uncertain.

Recent publications[12,13] suggest that clinicians may reduce stroke risk more effectively by targeting systolic blood pressure (SBP) variability along with SBP level using specific classes of antihypertensive drugs. These recommendations[12,13] originated mainly from clinical trials, which included high-risk groups, such as elderly[14,15] or hypertensive[16] patients or participants with a previous ischaemic stroke or transient ischaemic attack[14] or diabetes mellitus.[15,17] Other methodological issues that may have introduced bias are non-randomization, possible lack of power,[5,17] short follow-up time,[17] categorization of continuous variability measures for risk prediction,[8,14] the use of variability measures that are dependent on the level of blood pressure,[8,15] limited adjustment[14] or failure to account for reverse causality.[18] These factors render the current evidence on the prognostic significance of BPV inconclusive, especially in the general population.

"Controversy on blood pressure variability"

In this minireview we address the predictive value of BPV, over and beyond level of pressure, in randomly selected population samples. All reviewed studies had sufficient power,

Correspondence: Professor JA Staessen, Studies Coordinating Centre, Campus Sint Rafaël, Block d, Box 7001, Kapucijnenvoer 35, BE-3000 Leuven, Belgium. Email: jan.staessen@med.kuleuven.be. This paper has been peer reviewed. Received 24 December 2012; revision 29 March 2013; accepted 4 April 2013.

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List of abbreviations:

ARV	average real variability	MMD	difference between maximum and minimum blood pressure
BPV	blood pressure variability	VIM	variability independent of the mean

long follow-up duration and a wide age range. In addition, the conclusions are based mainly on novel indices of BPV, as assessed by conventional sphygmomanometry, self-measurement at home or 24 h ambulatory monitoring.

MEASURES OF BPV

Historical perspective

In the early 1970s, Clement *et al.*[19] assessed variability from the standard deviation (SD) and coefficient of variation (CV) of blood pressure measurements obtained every 5 min for 3 h in 70 untreated hypertensive patients. In that study, a positive relationship between sympathetic activity and the SD of blood pressure was observed. Blood pressure level and SD were also correlated. The CV was not correlated with various indices of sympathetic activity. In the early 1980s, Mancia *et al.*[20,21] analysed 24 h continuous intra-arterial recordings and showed that SD was positively correlated with blood pressure level and fell with antihypertensive drug treatment, whereas CV was independent of level irrespective of drug intervention.[21] Notwithstanding these initial findings, the same group used SD rather than CV to estimate the association between BPV and target organ damage on the incidence of cardiovascular complications.[22,23] These results were biased by blood pressure level.[22,23]

New indices of BPV

Recently Mena *et al.*[24] proposed average real variability (ARV) as a novel index representing short-term, reading-to-reading, within-subject variability in blood pressure. The ARV attempts to correct for the limitations of the commonly used SD, which accounts only for the dispersion of values around the mean and not for the order of the blood pressure readings.[11,24,25] The ARV is calculated by the following formula:

$$\mathrm{ARV} = \frac{1}{\sum w}\sum_{k=1}^{n-1} w \times |BP_{k-1} - BP_k|$$

where k ranges from 1 to $n - 1$, w is the time interval between BP_k and BP_{k+1} and n is the number of blood pressure readings.

Rothwell *et al.* proposed BPV independent of the mean (VIM) as a new index,[12,14] which may be a better predictor of cardiovascular outcome. The blood pressure VIM[12,14] is calculated as the SD divided by the mean to the power x and multiplied by the population mean to the power x. The power x is obtained by fitting a curve through a plot of SD against mean using the model $\mathrm{SD} = a \times \mathrm{mean}^x$, where x was derived by non-linear regression analysis.

"New indices of blood pressure variability"

Finally, some investigators also proposed maximum minus minimum blood pressure (MMD) as an index of BPV.[26,27]

VARIABILITY OF CONVENTIONAL BLOOD PRESSURE

We investigated the predictive value of BPV in a family-based randomly selected representative sample from the general population in Belgium with sufficient power, follow-up time and a wide age range ($n = 2944$; mean age 44.9 years; 50.7% women).[28] At baseline, trained nurses measured each participant's blood pressure at two home visits at an interval of 2–4 weeks. At each home visit, after the participants had rested for 5 min in the sitting position, the nurses obtained five consecutive blood pressure readings to the nearest 2 mmHg using mercury sphygmomanometers. We implemented a stringent programme for quality assurance and quality control. Every 3 months, the observers had to pass a test requiring them to read blood pressures from a videotape featuring a falling mercury column with Korotkoff sounds. Their readings had to comply within 5 mmHg of those of senior medical staff. Digit preference was checked at 6 monthly intervals.

We assessed within-subject overall (10 readings), within- and between-visit systolic BPV from VIM, MMD and ARV. Over a median follow up of 12 years, 401 deaths occurred and 311 participants experienced a fatal or non-fatal cardiovascular event. Overall mean (± SD) systolic BPV was 5.45 ± 2.82 units, 15.87 ± 8.36 mmHg and 4.08 ± 2.05 mmHg for VIM, MMD and ARV, respectively. Female gender, older age, higher mean SBP, lower body mass index, a history of peripheral arterial disease and the use of beta-blockers were the main correlates of systolic BPV. In multivariable-adjusted analyses, overall and both within- and between-visit BPV did not predict total or cardiovascular mortality or the composite of any fatal plus non-fatal cardiovascular end-points. For example, the hazard ratios (HR) for all cardiovascular events combined in relation to overall VIM, MMD and ARV were 1.05 (95% confidence interval (CI),

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0.96–1.15), 1.06 (95% CI 0.96–1.16), and 1.08 (95% CI 0.98–1.19), respectively. In contrast, mean SBP was a significant predictor of all end-points under investigation, independent of BPV (Fig. 1). In conclusion, in an unbiased population sample, BPV derived from conventional blood pressure readings did not contribute to risk stratification over and beyond mean SBP.[28]

VARIABILITY OF SELF-MEASURED BLOOD PRESSURE

Self-measured home blood pressure offers several of the well-recognised advantages of the more complex approach of ambulatory monitoring.[29–31] The greater number of readings and the minimisation of the white coat effect, observer bias and measurement error all contribute to a better diagnostic accuracy compared with office blood pressure measurement. Similar to visit-to-visit variability in the conventional clinic blood pressure,[14] multiple home blood pressure measurements[32–34] provide information on the day-to-day BPV in the relatively controlled home environment.

In 2008, we assessed self-measured home BPV in the Ohasama population, using the within-subject SD of the morning

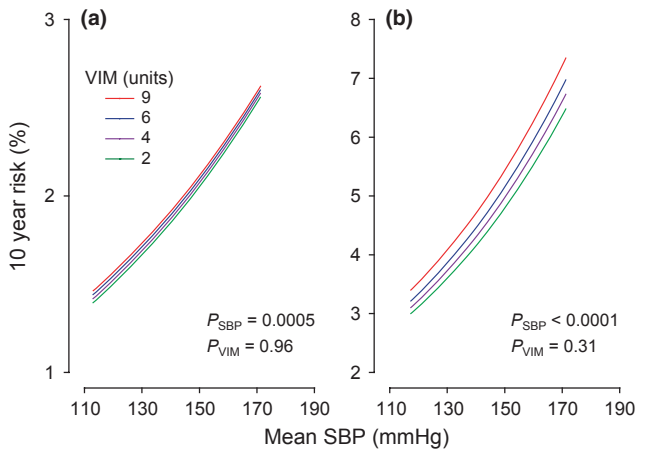

Fig. 1 Absolute 10 year risk of (a) death and (b) cardiovascular events in relation to mean systolic blood pressure (SBP) at different levels of overall systolic variability independent of the mean (VIM).[28] Mean SBP along the *x*-axis covers the 5th–95th percentile interval. The VIM is presented by four risk functions corresponding with 2, 4, 6 and 9 units (approximate quartile mid-points). The risk functions were standardized to the distributions (mean or ratio) of sex, age, body mass index, heart rate, smoking and drinking, total : high-density lipoprotein serum cholesterol ratio, plasma glucose, history of cardiovascular disease and the use of beta-blockers. Among 2944 participants, 401 deaths and 311 composite cardiovascular end-points occurred. P_{SBP} and P_{VIM} indicate the significance of mean SBP and the overall VIM. Reproduced with permission from Schutte *et al.*[28]

SBP over 26 days (median) of self-measurement.[34] In multivariable-adjusted Cox models also including blood pressure level, a 1 – SD increase in the between-subject variability was associated with a higher risk of total mortality (HR 1.18; 95% CI, 1.07–1.31), cardiovascular mortality (HR 1.20; 95% CI 1.02–1.40), non-cardiovascular mortality (HR 1.18; 95% CI 1.04–1.34) and stroke mortality (HR 1.38; 95% CI 1.12–1.72), but not cardiac mortality (HR 1.02; 95% CI 0.81–1.29). Cardiac mortality included deaths from coronary heart disease and heart failure. Cardiovascular mortality comprised the aforementioned end-points plus fatal stroke. The association of BPV with non-cardiovascular mortality was difficult to interpret, but may reflect reverse causality, subclinical disease leading to greater variability.

More recently, the Finn-Home investigators reported that day-to-day variability of the self-measured SBP in the morning, estimated from the within-participant SD over 7 days, predicted total mortality and cardiovascular events.[6] The HR expressing incremental risk of total mortality and cardiovascular events for a 1 mmHg between-subject increment in variability was 1.05 (95% CI 1.02–1.09; $P = 0.006$) and 1.04 (95% CI 1.00–1.07; $P = 0.03$), respectively.[6] Day-to-day variability in the evening SBP was not predictive ($P \geq 0.11$).[6] Ushigome *et al.* showed significant correlations between CV of self-measured home blood pressure and macroalbuminuria in Type 2 diabetes mellitus.[35] However, SD, CV and ARV of self-measured home blood pressure did not predict the progression of chronic kidney disease reported by Okada *et al.*[36]

"Variability of self-measured blood pressure"

We explored whether new indices of BPV derived from the self-measured home blood pressure predicted outcome.[37] We analysed mortality and stroke risk in 2421 Ohasama residents and excluded high-risk subjects with a previous stroke. In the Ohasama study, physicians and public health nurses instructed participants how to measure their home blood pressure using a validated oscillometric device (OMRON HEM 401C; Omron Healthcare, Kyoto, Japan). Participants were asked to record their blood pressure for 4 weeks: (i) after at least 2 min rest in the morning within 1 h of waking and, if applicable, before taking their blood pressure-lowering medications; and (ii) in the evening just before going to bed. The first reading obtained on each occasion was used for analysis. We assessed the independent predictive value of the within-subject mean SBP and corresponding variability as estimated by variability independent of the mean (VIM), difference between maximum and minimum blood pressure (MMD) and ARV. Over a median of 12.0 years, 412 participants died (139 of cardiovascular causes) and 223 had a stroke. In multivariable-adjusted Cox models including morning systolic pressure: (i) VIM and ARV predicted total and

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cardiovascular mortality in all participants ($P \leq 0.044$); (ii) VIM predicted cardiovascular mortality in treated ($P = 0.014$), but not in untreated ($P = 0.23$) participants; and (iii) morning MMD did not predict any end-point ($P \geq 0.085$). In models already including evening systolic pressure, only VIM predicted cardiovascular mortality in all and in untreated participants ($P \leq 0.046$). Figure 2 shows the multivariable-adjusted 10-year risk of a cardiovascular death in relation to the mean level and VIM of morning SBP in all participants. Morning SBP was a consistent predictor of stroke and cardiovascular mortality ($P \leq 0.0049$), with the exception of cardiovascular mortality in treated participants ($P = 0.082$).

The R^2 statistic, a measure of the incremental risk explained by adding BPV to models already including SBP and covariables, ranged from < 0.01% to 0.88%. In conclusion, in a Japanese population, the new indices of BPV derived from self-measured home blood pressure did not incrementally predict outcome over and beyond mean systolic pressure. Being on antihypertensive drug treatment seemed to be the main driver of the significant associations between cardiovascular mortality and BPV.[37]

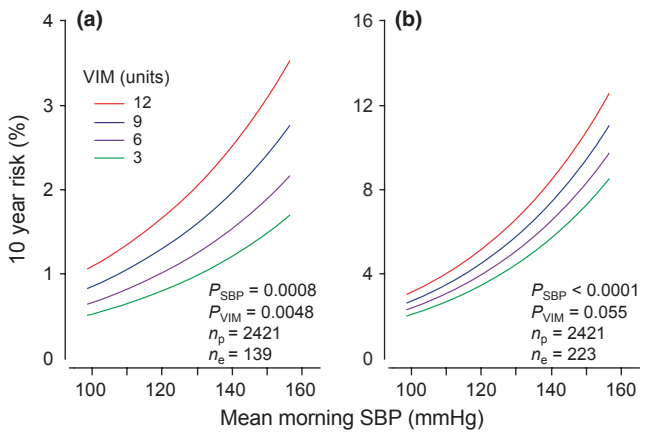

Fig. 2 Absolute 10 year risk of (a) cardiovascular mortality and (b) stroke incidence in relation to the mean level of systolic blood pressure (SBP) measured at home in the morning in 2421 participants.[36] The analyses were standardized to the distributions (mean or ratio) of sex, age, body mass index, heart rate, smoking and drinking, total cholesterol, diabetes mellitus, history of cardiovascular diseases and treatment with antihypertensive drugs. In each panel, mean SBP along the *x*-axis covers the 2.5th–97.5th percentile interval. Four continuous lines represent the risk independently associated with variability independent of the mean (VIM) equal to 3, 6, 9 and 12 units. *P*-values are for the independent effect of SBP (P_{SBP}) and VIM (P_{VIM}); n_p and n_e indicate the number of participants at risk and the number of events, respectively. Reproduced with permission from Asayama *et al.*[36]

VARIABILITY OF AMBULATORY PRESSURE

Sleep–trough and pre-awakening morning surge

Kario *et al.*[38] introduced the definitions of the sleep–trough and pre-awakening morning surge in blood pressure. They compared the risk of silent and clinical cerebrovascular diseases in 53 hypertensive (assessed by clinic measurement) patients of the top decile (≥ 55 mmHg) of the systolic sleep–trough morning surge with the risk in the other 466 patients. The risk of multiple brain infarcts was approximately twofold higher in patients belonging to the top decile of the systolic sleep–trough morning surge. The morning surge remained a significant predictor of stroke even after adjustment for the 24 h blood pressure, nocturnal dipping status and the prevalence of silent infarcts at enrolment.[38] However, these findings are not supported by the recent publication by Verdecchia *et al.*[39] who investigated the relationship between the day–night blood pressure dip and the early morning surge in a cohort of 3012 initially untreated subjects with essential hypertension. In that population, the magnitude of blood pressure dip from day to night (night-to-day ratio) was directly associated with the magnitude of the blood pressure surge in the early morning; the day–night reduction in SBP showed a direct association with the sleep–trough ($r = 0.564$; $P < 0.0001$) and the pre-awakening ($r = 0.554$; $P < 0.0001$) SBP surge.[39] Over a mean follow-up period of 8.44 years, 268 subjects had a cardiovascular event and 220 subjects died. A blunted sleep–trough (≤ 19.5 mmHg; the lowest quartile) and pre-awakening (≤ 9.5 mmHg) blood pressure surge were both associated with an excess risk of events (HR 1.66 (95% CI 1.14–2.42) and 1.71 (95% CI 1.12–2.71), respectively). However, neither patients with a high sleep–trough (> 36.0 mmHg; the highest quartile) nor those with a high pre-awakening (> 27.5 mmHg) systolic pressure had independent risks for mortality and cardiovascular events.

"Level is clinically important, not variability"

We analysed the sleep–trough and the pre-awakening morning surge in the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) study,[40] a large randomly recruited population sample from 11 centres.[11,40–42] We programmed portable monitors to obtain ambulatory blood pressure readings at 30 min intervals throughout the whole day or at intervals ranging from 15 to 20 min during the day and from 30 to 60 min at night. The devices implemented an auscultatory algorithm (Accutracker II; SunTech Medical Instruments, Raleigh, NC, USA) in Uppsala[43] or an oscillometric technique (SpaceLabs 90202 and 90207 (Spacelabs Healthcare, Snoqualmie, WA, USA), Takeda TM-2421 recorders (A&D, Tokyo, Japan) and Nippon Colin ABPM-630 (Omron Colin, Tokyo, Japan)) in the other

cohorts.[44–50] When accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 1 000 to 2 000 h in Europeans[44,45,48,49] and South Americans,[46] and from 0800 to 1 800 h in Asians;[47,50] the corresponding night-time intervals ranged from 0000 to 0600 h and from 2 200 to 0400 h, respectively. Within individual subjects, we weighted the means of the ambulatory blood pressure level by the interval between readings. To quantify the nocturnal fall in blood pressure, we computed the night-to-day blood pressure ratio from the night-time and daytime blood pressures. During a median follow up of 11.4 years, 785 deaths and 611 fatal and non-fatal cardiovascular events occurred in 5645 IDACO participants (mean age 53.0 years; 54.0% women).[40] After accounting for covariables and the night-to-day ratio of systolic pressure, the HR of all-cause mortality was 1.32 (95% CI 1.09–1.59) in the top decile of the systolic sleep–trough morning surge (≥ 37.0 mmHg). For cardiovascular and non-cardiovascular deaths, these HR were 1.18 (95% CI 0.87–1.61) and 1.42 (95% CI 1.11–1.80), respectively. For all cardiovascular, cardiac, coronary and cerebrovascular events, the HR in the top decile of the systolic sleep–trough morning surge was 1.30 (95% CI 1.06–1.60), 1.52 (95% CI 1.15–2.00), 1.45 (95% CI 1.04–2.03) and 0.95 (95% CI 0.68–1.32), respectively. Furthermore, only in the

"Variability of ambulatory blood pressure"

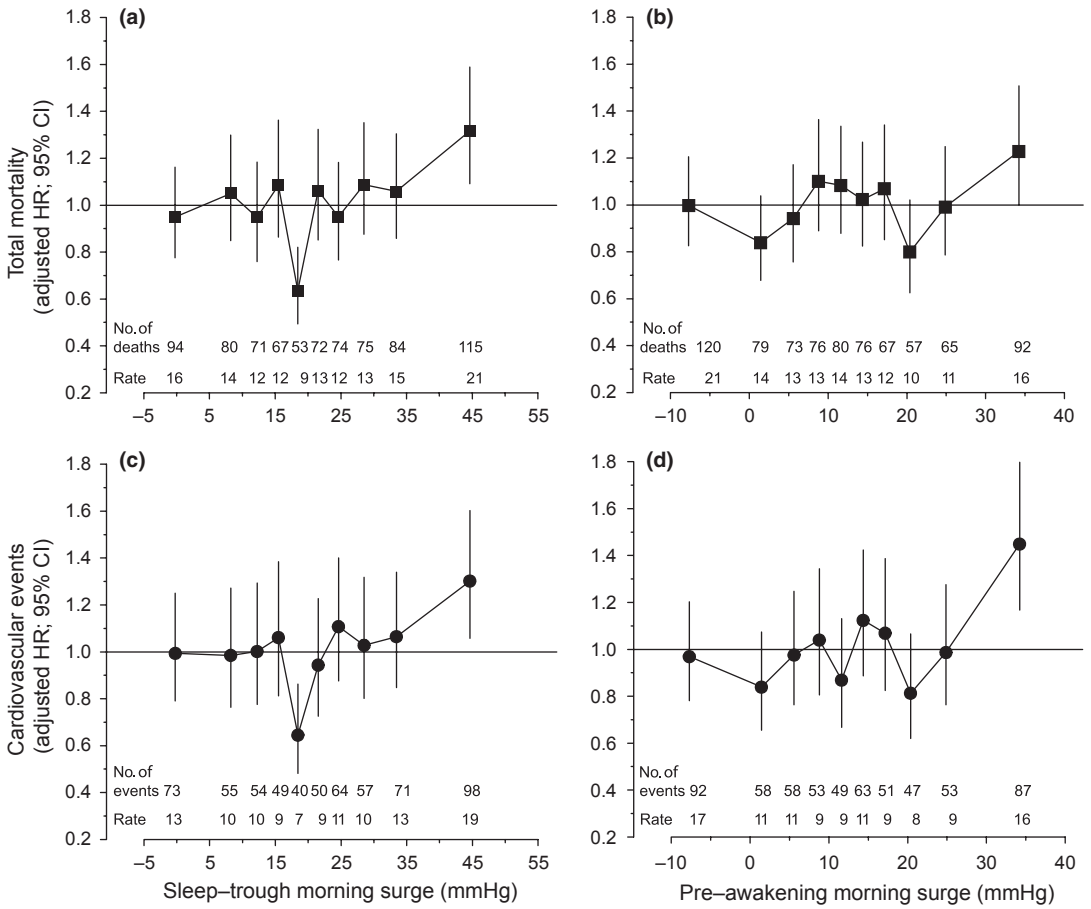

Fig. 3 Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for (a,c) all-cause mortality and (b,d) cardiovascular events by ethnic- and sex-specific deciles of the sleep–trough (a,b) and pre-awakening (c,d) morning surge in systolic blood pressure (SBP) in 5645 subjects.[40] The HR expresses the risk in deciles compared with the average risk in the whole study population and was adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, antihypertensive drug treatment, 24 h SBP and the systolic night-to-day blood pressure ratio. The number of events and incidence rates (events per 1000 person-years) are also given for each decile. Reproduced with permission from Li *et al.*[40]

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Table 1 Risk of a composite cardiovascular event explained by Cox regression[11]

	Systolic blood pressure			Diastolic blood pressure		
Model	−2 Log likelihood	*P*-value	R^2 (%) ratio	−2 Log likelihood	*P*-value	R^2 (%) ratio
Basic model*	10307.0	N/A	9.95	10307.0	N/A	9.95
+24 h blood pressure	10213.4	< 0.001	11.1	10258.2	< 0.001	10.6
+24 h blood pressure and ARV	10209.4	0.046	11.2	10250.6	0.006	10.7

*The basic Cox model was stratified for cohort and included sex, age, 24 h heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus and treatment with antihypertensive drugs as covariables.

P values are for the improvement of the fit across nested models.

Reproduced with permission from Hansen *et al.*[11]

N/A, not applicable.

"Level is clinically important, not variability"

top decile group was the risk significantly higher than the average risk in the whole population, whereas in the 50th percentile group the risk was significantly lower (by 35%; $P < 0.01$) for all-cause mortality and for all cardiovascular events (Fig. 3).[40] In conclusion, an exaggerated morning surge, exceeding the 90th percentile of the population, significantly and independently predicted cardiovascular outcome and may contribute to risk stratification by ambulatory blood pressure monitoring.

Several studies have explored why the morning surge in blood pressure is difficult to use to stratify risk in clinical practice. First, using the morning surge in blood pressure requires multiple blood pressure readings during sleep and during the pre-awakening and awakening periods. Second, subjects have to complete a diary during ambulatory blood pressure monitoring to report the sleeping and awake periods. In our database, these two issues eliminated 4 850 of 11 786 available subjects. Finally, in older patients with isolated systolic hypertension,[51] the morning surge in blood pressure, irrespective of its definition, was poorly reproducible. Nearly 30% of subjects changed their surge status either in the short term (median 33 days) or in the long term (median 10 months).[51]

Average real variability in ambulatory pressure

To address the prognostic value of short-term BPV, we assessed BPV from the SD and ARV in 24 h ambulatory blood pressure recordings in the IDACO study,[11,40–42] specifically 8 938 participants (mean age 53.0 years; 46.8% women) who were followed up for a median of 11.3 years.[11] Participants with a higher BPV were older, had higher blood pressure, were more likely to be male and to have diabetes mellitus. Higher diastolic ARV in 24 h ambulatory blood pressure recordings predicted ($P \leq 0.03$) total (HR 1.13; 95% CI 1.07–1.19) and cardiovascular (HR 1.21; 95% CI 1.12–1.31) mortality and all types of fatal combined with non-fatal end-points (HR ≥ 1.07), with the exception of cardiac and coronary events (HR ≤ 1.02; $P \geq 0.58$). Higher systolic ARV in 24 h ambulatory blood pressure recordings predicted ($P < 0.05$) total (HR 1.11; 95% CI 1.04–1.18) and cardiovascular (HR 1.17; 95% CI 1.07–1.28) mortality and all fatal combined with non-fatal end-points (HR ≥ 1.07), with the exception of cardiac and coronary events (HR ≤ 1.03; $P \geq 0.54$). The SD predicted only total and cardiovascular mortality. After accounting for the 24 h blood pressure level, ARV in 24 h ambulatory blood pressure recordings added only 0.1% to the prediction of a cardiovascular event (Table 1). Sensitivity analyses considering ethnicity, sex, age, previous cardiovascular disease, antihypertensive treatment, number of blood pressure readings per recording or the night-to-day blood pressure ratio were confirmatory. Our report established that short-term reading-to-reading BPV is an independent risk factor, but moreover also highlighted that the level of the 24 h blood pressure remains the primary blood pressure-related risk factor to account for in clinical practice.

CONCLUSION

We assessed BPV derived from home visit,[28] self-measured home pressure[37] and ambulatory monitoring.[11,40] We estimated BPV (VIM, MMD and ARV) and the morning surge in blood pressure. None of these variability indices or morning surge in blood pressure substantially refined risk profiling over and beyond the blood pressure level. In risk stratification, clinicians should concentrate on blood pressure level, the predominant risk factor modifiable by lifestyle measures and antihypertensive drug treatment.

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